ADVANCED GASTRIC CANCER WITH LONG - TERM SURVIVAL FOR OVER TEN YEARS : REPORT OF A CASE

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Long-term survival is rare in patients with advanced gastric cancer because most of them die of tumor recurrence within two years after the curative surgery. Surgery continues to be the mainstay of treatment, although other nonsurgical treatments have been widely researched. We report a 58-year-old female patient with a scirrhous type advanced gastric cancer. She underwent a radical subtotal gastrectomy with Billroth II anastomosis. The surgical specimen showed an extensive submucosal and subserosal spreading, and 9 of the 34 dissected lymph nodes were involved. Thereafter, she received adjuvant chemotherapy with fluorouracil, adriamycin and mitomycin-C. She had regular follow-up thereafter. Ten years and six months later, by esophagogastroduodenoscopy, the patient was found to have a new growth tumor with only a small mucosal defect at the cardia of the remnant stomach. The patient received total resection of the remnant stomach, and the findings of the resected specimen showed an advanced scirrhous adenocarcinoma invading the whole stomach layers and the esophagus. Of the 33 resected lymph nodes, 18 of them were found positive for adenocarcinoma. This is a rare case of a patient with scirrhous gastric cancer with long-term survival, and adjuvant chemotherapy may attribute to such a clinical presentation.

Key words: gastric cancer, long-term survival, chemotherapy.

INTRODUCTION

Gastric cancer remains one of the leading causes of cancer related death worldwide, especially in highly prevalent areas. While the five-year survival rate of patients with early gastric cancer has been reported to be 90-95%, that for those with advanced gastric cancer ranges from 7.5 to 22.5%[1,2]. Histologically, the diffuse type tumors have worse prognosis. We reported a case of a patient who had diffuse type advanced adenocarcinoma of the stomach with lymph node metastasis. The patient developed another diffuse type remnant gastric cancer 10.5 years after treatment of the precedent cancer.

CASE REPORT

A 47-year-old female patient was admitted to the Taipei Medical College Hospital due to a nearly one-year history of persistent epigastric pain, and recent onset of poor appetite and body weight loss (3 kg in 10 days). On inquiry, there was no traceable cancer risk factor.

On admission, the patient had a mildly pale

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conjunctivae and tender epigastrium. The laboratory examinations showed hemoglobin, 10.4 g/dl (normal range, 12-14g/dl); MCV, 84.1 fL (81-99 fL for female); RBC, 3,830,000 (4,200,000-5,400,000); carcinoembryonic antigen (CEA), 0.23 ng/ml (0-3 ng/ml for non-smokers); and alfa-fetoprotein, 1.28 ng/ml (0-20 ng/ml). The result of the esophagogastroduodenoscopy (EGD) revealed a Borrman type 2 gastric cancer, with a large ulcerating tumor located in the gastric angle extending proximally to the lower body. The pathologic examination disclosed poorly differentiated adenocarcinoma with signet ring cells. The upper gastrointestinal series showed an ulcerative infiltrative type gastric cancer with a big area of mucosa destruction, which mainly involved the lesser curvature of the antrum, angle and lower body (Fig. 1). The enhanced abdominal computed tomography (CT) scan showed gastric body wall thickening and lymphadenopathy in the gastrohepatic ligament region.

The patient underwent a subtotal gastrectomy with Billroth II anastomosis and a radical D2 dissection one week later. The postoperative diagnosis was a H0P0N1, Bormann type 2 gastric cancer. The cut surface of the surgical specimen showed an ill-defined white tumor invading through the muscular layer. The resected greater omentum and the duodenal cuff were essentially normal. Microscopically, it revealed a scirrhous anaplastic adenocarcinoma of the stomach with marked submucosal and subserosal spreading. Nine of the 34 resected lymph nodes showed metastasis (Fig. 2).

The patient received the first of the six courses of adjuvant chemotherapy with fluorouracil, adriamycin and mitomycin-C (FAM) one month after surgery. The patient had periodical follow-up in the subsequent years. She underwent abdominal sonogram and EGD every six months and abdominal CT scan yearly for 5 years. None of them showed evidences of tumor

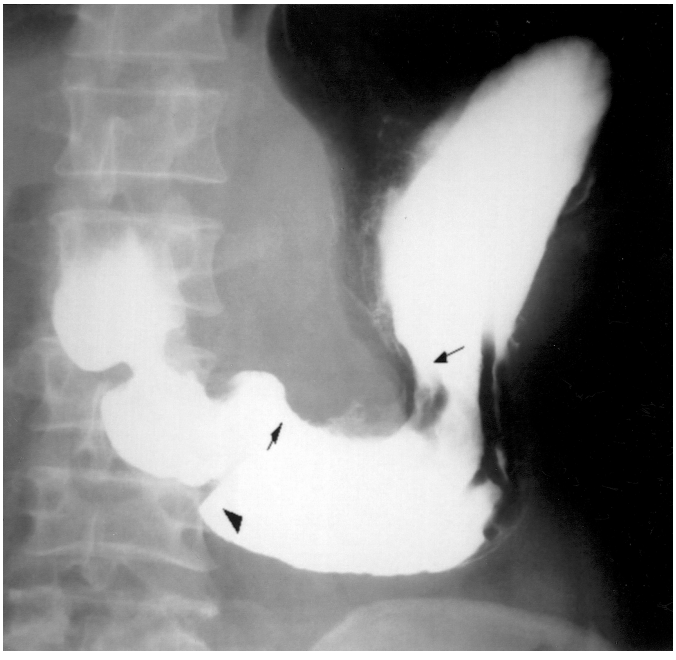

Fig. 1. The upper gastrointestinal series shows an area of mucosal destruction involving mainly the lesser curvature of body and proximal antrum (arrows). The the incisura angularis appeared persistently widened and rigid. The arrowhead shows a fold converging to the lesion.

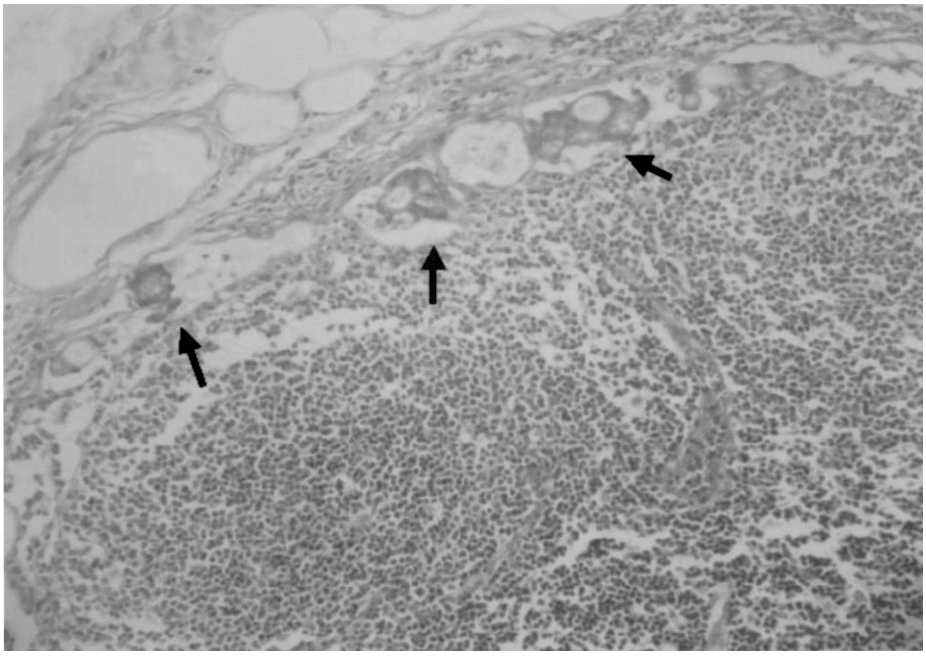

Fig. 2. Dissected lymph node with at least three tumor nests (arrows) in the marginal sinuses. (H&E, x 200).

recurrence. The serum CEA levels were checked every three months. Isolated episodes of CEA elevations were noted at the 7th month (before the last of the six courses of chemotherapy), 11th month and 25th month after surgery, respectively (Fig. 3).

The patient's condition had been relatively stable until May 2002, 10.5 years (126 months) after her surgery. She had dysphagia, acid reflux and weight loss of 6 kg in a few months. The EGD revealed a small and depressed lesion with superficial erosion and reddish discoloration at the cardia of the remnant stomach (Fig. 4). The biopsy specimens proved an adenocarcinoma with signet ring cells. Her hemoglobin level was 8.0 g/dl. The tumor markers remained within the normal limits. The upper gastrointestinal series and the CT scan showed concordant imaging findings.

She underwent a radical total gastrectomy with esophagojejunostomy, splenectomy and lymph nodes dissection. There was severe adhesion, as well as a small metastatic nodule at the jejunal mesentery, 20 cm distal to the gastrojejenostomy. The pathological results of the surgical specimens showed a poorly differentiated adenocarcinoma with signet ring cells involving the resected esophagus and the remnant stomach. Of the 33 removed lymph nodes, 18 were found positive for cancer.

The endoscopically detected mucosal defect of tumor was mainly located at the cardia, where only a few superficial ulcerations could be seen on the gross specimen. Proximally, the esophageal mucosa was essentially normal, although there was a prominent submucosal invasion extending to the resection margin by the gastric cancer (Fig. 5). Distal to the superficial ulcerations, the remnant stomach also showed diffuse mucosal involvement and an extensive submucosal infiltration of cancer (Fig. 6). Only minimal portion of the gastro-jejunal area was involved by the tumor (Fig. 7).

After her second surgery, she received adjuvant chemotherapy as before (etoposide, leucovorin, fluorouracil and mitomycin-C). However, the condition deteriorated and the patient passed away two years later, as the disease progressed.

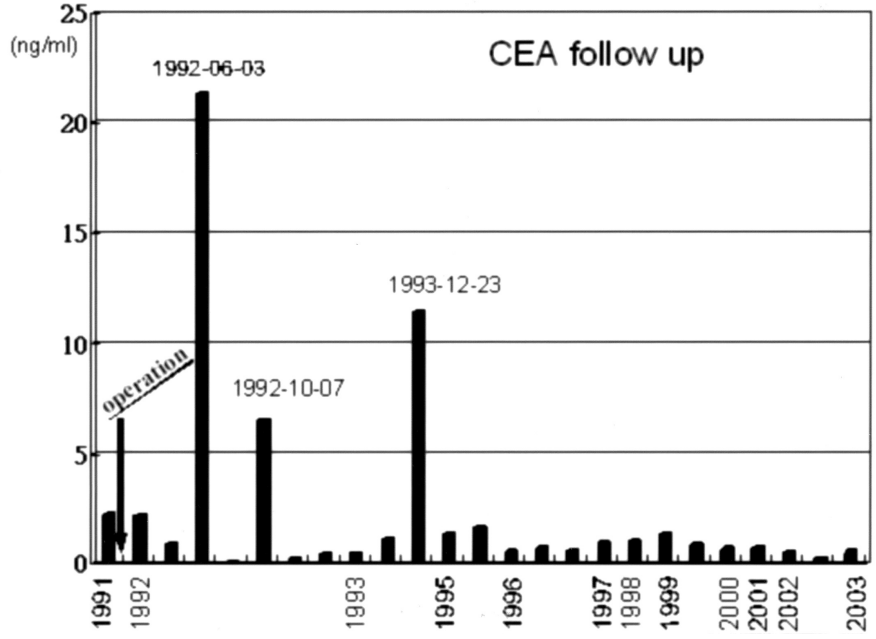

Fig. 3. The pre-operative level of carcinoembryonic antigen (CEA) was low during most of the post-operative period. There were three peaks noted at the 7th, 11th and 25th months after the first surgery.

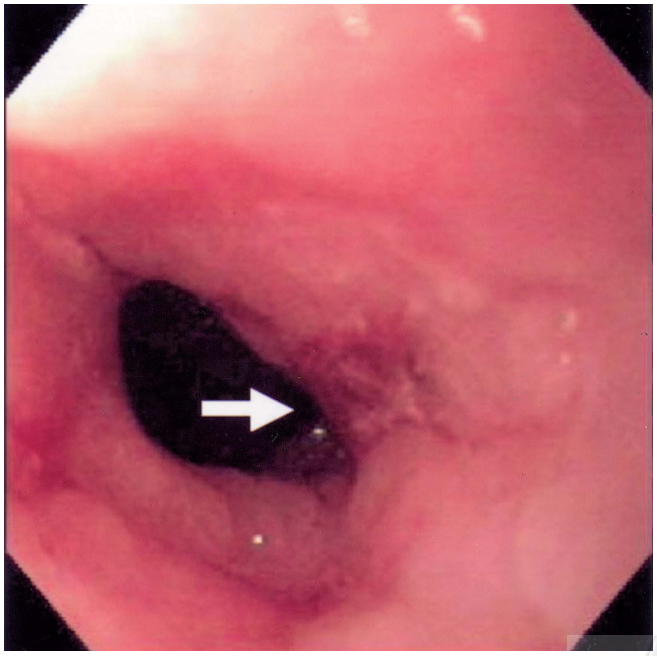

Fig. 4. The endoscopic examination showed a small depressed lesion with superficial erosion (arrow) and surrounding redness at the cardia of the remnant stomach.

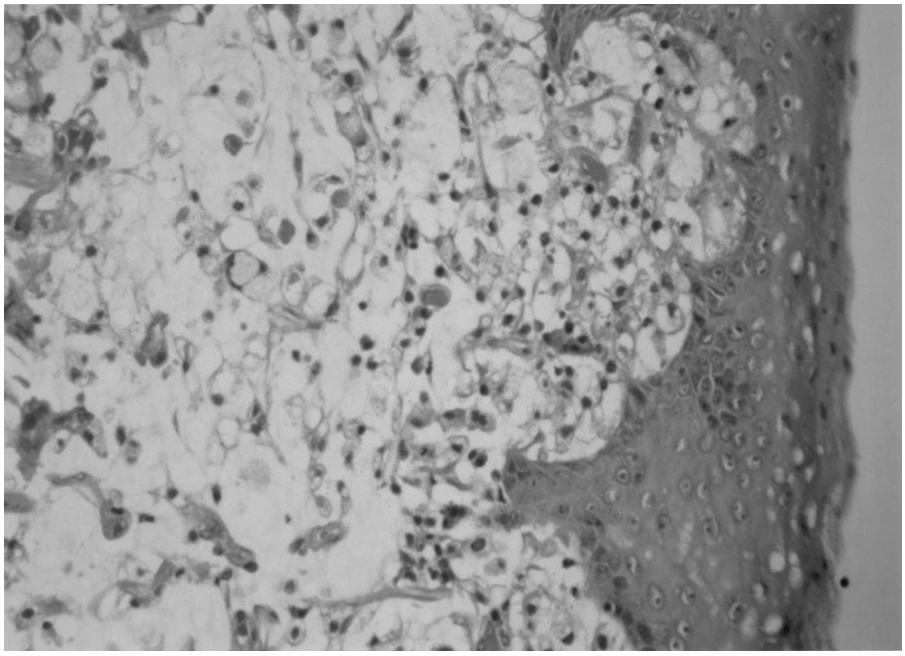

Fig. 5. Adenocarcinoma with signet ring cells infiltrating the submucosal layer of esophagus. (H&E, x 400).

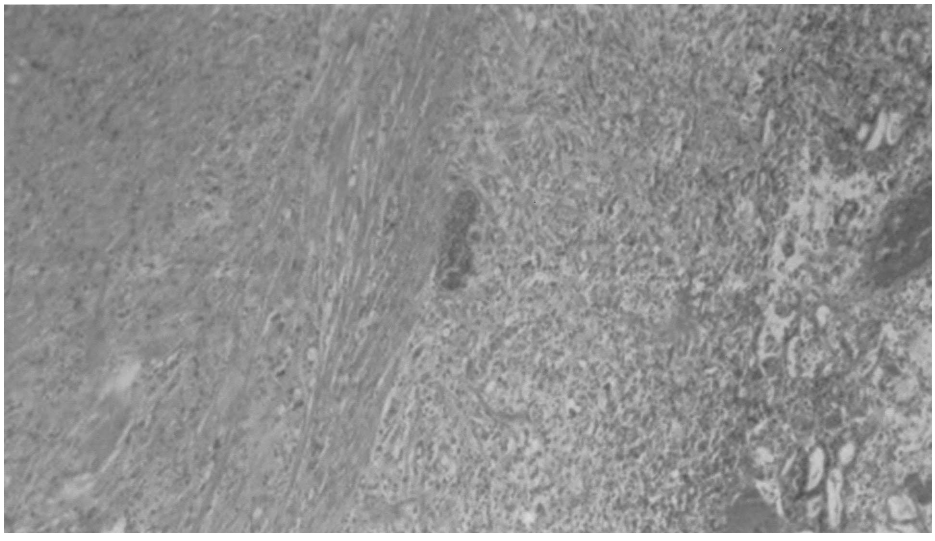

Fig. 6. Poorly differentiated adenocarcinoma infiltrating the whole layer of stomach. (H&E, x 100).

DISCUSSION

The overall 5-year-survival rate in patients with advanced gastric cancer is 22.2% and 24.9%, for man and woman, respectively, in the United States[1], and that is 40-60% in Japan[2]. Despite of multiple treatment modalities, achieving a long-term survival of advanced gastric cancer is still difficult.

Adachi et. al described the characteristics of patients with long-term survival after resection for advanced gastric carcinoma[3]. By analyzing 126 eligible patients, those with long-term survival had

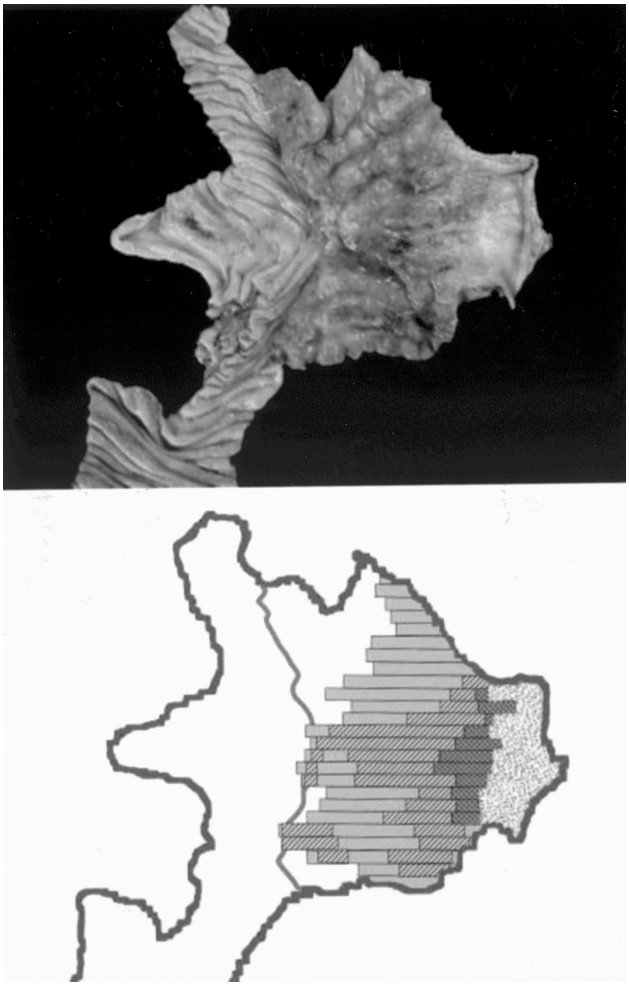

Fig. 7. The surgical specimen shows a small ulceration of the cancer, while the remaining gastric stump consists of a non-ulcerative portion with mucosal or an extensive submucosal involvement. Most of the anastomosis with jejunum was spared.
Esophagus with submucosal infiltration.
Gastric cardia with whole layer involvement and superficial ulcerations.
Gastric stump with whole layer involvement but without erosion.
Gastric stump with intact mucosa and an extensive submucosal infiltration.

smaller tumor size (< 4 cm), lack of serosal invasion, limited number of positive lymph nodes and earlier stage of disease. Our patient had all the features except for the lack of serosal involvement.

In patients with advanced gastric cancer, non-surgical therapeutic modalities have been more and more emphasized. Macdonald et al. showed increased survival rate in patients who received adjuvant chemotherapy with fluorouracil plus leucovorin and radiation[4]. In fact, prevention or reduction of the tumor recurrence is probably more important than its early detection, because the findings of most diagnostic tests (tumor markers, sonograms, CT or endoscopy) failed to detect the recurrence at the asymptomatic phase[5,6]. Another possible explanation is because effective treatment strategy is not available once

recurrence occurs[7]. In our patient, the adjuvant chemotherapy might have caused two possible consequences: if the cancer is a new-growth tumor, the chemotherapy should have caused a complete cure; or, if it is a recurrent tumor, then the chemotherapy should have induced a very prolonged dormant phase.

Chemotherapy is critical to exert the direct cytotoxic effect of the drug for the so-called "tumor dormant therapy"[8]. Chemotherapy causes "tumor dormancy" probably by inhibiting neovascularization. Although cancer cells cannot be completely killed, keeping the malignant cells "quite" can stabilize tumor burden and prolong patient's survival time. However, most anti-cancer drugs used nowadays are cytotoxic but not anti-angiogenic. Factors such as adhesion molecules, metastasis suppressing genes, tumor cell motility and immune response may play a definite role in the development of metastases of highly vascularized primary tumor, after a period of tumor dormancy [9,10]. What is known about the dormancy is still limited, but some of the above-mentioned factors could have influenced patient's long-term survival.

While it is hard to determine whether our patient had a "new growth" or "recurrent" cancer, it would be indeed academically interesting to do so. Evidences supporting a new growth tumor include the time of occurrence (the tumor developed 10.5 years after the first surgery) and the location of the second gastric cancer, which probably had arisen from the cardia, as shown on the mapping. However, the scirrhous histologic features lead to the possibility of recurrence. Advances in molecular biology might help to clarify this issue. Kawamura et al. concluded that microsatellite instability, also known as MSI, was present in 30% of patients with recurrent disease, but absent in those with non-recurrent tumor. Furthermore, MSI-H was observed only in patients with recurrent disease. This feature might help in differentiating a recurrent tumor from a new grown one. Also, these results implied there may be different pathways of carcinogenesis between recurrent and non-recurrent tumors[11].

CEA is one of the most studied markers for gastrointestinal tumor. CEA is normally found in the mucous secretions of the stomach, small bowel and biliary tract. CEA level may be influenced by tumor production, tumor volume, transport of CEA from tumor to systemic circulation, CEA metabolism in the liver, etc. CEA levels are usually lower in gastric cancer cells with poor differentiation[12]. CEA is localized on membrane and accumulated into the cell in this condition[13]. Clinically, the CEA is used to monitor treatment response and detect recurrence. The CEA levels tend to remain low if the preoperative value is low. Image studies are necessary for a more satisfactory surveillance under such circumstances[14].

CEA is metabolized in liver and its levels remain low unless liver or lymph node metastasis occurs. Isolated elevation of CEA may not be significant and the study should be rechecked. CEA may become elevated in patients undergoing adjuvant chemotherapy without evidence of cancer recurrence. This is most likely due to the hepatic toxicity of the administered drug, like fluorouracil and levamisol[15]. At the same time, a cancer tissue can be composed of different cell types, with different degree of differentiation, and CEA production[16]. CEA production by the tumor itself is the major factor determining the serum CEA level[17]. A persistent elevation frequently heralds clinical evidence of recurrent disease. The three isolated elevations of CEA may be related to one of the explanations above mentioned. What we are sure is, none of such elevations is related to tumor recurrence, as the patient had a new tumor much later.

In summary, we presented a case of a patient with advanced gastric cancer with long-term survival. Despite of the time of occurrence and the location, we hypothesize that our patient might have a recurrent gastric cancer. While the surgery reduced the tumor bulk, the adjuvant chemotherapy could have induced a dormant state to the few foci of cancer tissue occult in the remnant stomach. Microsatellite instability might have played a role in the pathogenesis of the recurrent tumor. With no means to reduce the role of surgery,

other non-surgical therapeutic modalities should be seriously considered in every patient with advanced gastric cancer.

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進行性胃癌合併十年半的長期存活：一病例報告

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胃癌仍爲我國癌症致死之主要原因之一。 近年來外科醫師對於開刀方式的研究及進展試圖改善胃癌病患的長期存活率，但胃癌的復發率仍然偏高，其中原因可能和腫瘤本身之臨床及病理特徵有關。胃癌的復發多在開刀後之二年內發生，多半和遠端轉移、Scirrhous 型之病理型態 (硬胃癌)、胃漿膜之侵犯以及腹膜轉移有著密切之關係。另外女性也是復發的危險因子之一。個案是一位 58歲之女性病患，在1991年10月(病人當時年齡爲46歲)被診斷有scirrhous 型態之進行性胃癌。病人因此接受亞全胃切除併畢洛氏第二型胃十二指腸接合術。手術標本發現除黏膜及漿膜下層之蔓延外，在 34 顆取下之淋巴結節中有 9顆受到腫瘤的侵犯。病人在術後接受以 fluorouracil、adriamycin 和 mitomycin-C爲主的輔佐性化學治療及定期門診追蹤。 追蹤方式包括CEA 腫瘤指數監測、腹部超音波、斷層掃瞄及上消化道內視鏡。在經過十年又六個月的時間 (2002年 4月)，病患又被發現一個位於賁門，黏膜缺陷不大之惡性病變。殘餘胃的全胃切除再度顯示硬胃癌，其侵犯範圍包括全胃壁、食道及33顆被切除之18顆淋巴節，其中也包括一個位於空腸附近之結節。藉著 mapping 發現主要病灶之位置乃來自賁門而非開刀接合處。 從腫瘤的臨床表現，我們認爲這位病人在10.5年後所再得的胃癌可能爲一個復發癌，且輔助性化療可能是造成病患長期存活的主因之一。

關鍵語：胃癌，長期存活，化療